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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/654,328	09/01/2000	Michael B. Brenner	B0801/7187(ERP/MAT)	5793

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/654,328	Applicant(s) BRENNER ET AL.	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-9,13,16,22,24,25,30,35,36,44-46,48 and 49* is/are pending in the application.

4a) Of the above claim(s) *7,9,13,22,24,25,30,35,36,46,48 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6,8,16,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5 & 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1, 3, 5-9, 13, 16, 22, 24, 25, 30, 35, 36, 44-46, and 48-49 are pending.

2. Claim 3 was inadvertently omitted from the restriction, upon reconsideration Examiner included claim 3 with Group I as the claims are drawn to a method of treating a subject having an inflammatory joint disorder by administering an antibody to cadherin 11.

3. Applicant's election of Group I (Claims 1, 3, 5-6, 8, 16 and 44-45), drawn to a method of treating a subject having an inflammatory joint disorder by administering an antibody to cadherin-11, filed on 2-20-02, is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants further elect "integrin" as the counter receptor and "factor secretion" as the cellular functions as species. Upon reconsideration Examiner has extended the prior art search to cover a method for treating a subject having an inflammatory joint disorder wherein the cadherin-11 counter-receptor is a cadherin and the cellular function is cell proliferation.

4. Claims 7, 9, 13, 22, 24, 25, 30, 35, 36, 46, 48 and 49 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

5. Claims 1, 3, 5-6, 8, 16, and 44-45 are under consideration in the instant application as they read on a method for treating a subject having an inflammatory joint disorder using antibody as cadherin-11 inhibitory agent.

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Inventor Xavier Valencia citizenship has been altered without being dated or initialed.

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification on page 24, lines 12 and 13 contain embedded hyperlinks and/or other forms of browser-executable code which are impermissible and require deletion.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3, 5, 6, 16 and 44-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a subject having a rheumatoid arthritis disorder comprising administering locally to a synovium of the subject an anti cadherin-11 monoclonal antibody does not reasonably provide enablement for a method for treating a subject having any inflammatory joint disorder comprising administering any cadherin-11 agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention without any undue amount of experimentation.

Besides anti cadherin-11 monoclonal antibody, the specification fails to provide any guidance as to how to make and how to use any "cadherin-11 inhibitory agent.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Applicant has not provided sufficient biochemical information that distinctly identifies such "inhibitory agents" other than monoclonal antibodies aganist cadherin-11. While any "cadherin-11 inhibitory agent" may have some notion of the activity of the "inhibitory agent", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The specification (page 15, lines 24-34, page 19, lines 17-32, page 22, lines 5- 28 and page 28, lines 2-10) fails to provide any guidance on how to make any antibody, any cadherin 11 polypeptide, any nucleic acid molecule, or any antisense molecule that can be used to treat a subject having any inflammatory joint disorder.

There is insufficient guidance as to which amino acid segments within the polypeptide can be unique and retain a distinct functional capability of the full length polypeptide. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid fragment can retain the functional capabilities of the full length polypeptide requires knowledge of, and guidance with regard to, which segments in the polypeptide's sequence contribute to its function.

Minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Therefore, structurally unrelated compounds comprising any "cadherin-11 inhibitory agent" would be expected to have greater differences in their activities.

The scope of the instant claims encompasses any antisense cadherin-11 inhibitory agent from cadherin-11 nucleic acids SEQ ID NO:1 of 10, 15 or 15-20 bases, as disclosed in the specification at page 28. "Antisense" therapy is well known in the art to be highly unpredictable, even though the level of skill in the art is high. For instance, Mountain reviews in Trends Biotechnol (18:119-128, 2000) that while much progress has been made in the field of gene therapy, developing effective gene therapies is much more demanding than originally anticipated (e.g., pg 120, middle); and that most of the difficulty lies with the development of effective vectors since the vectors in use all have both advantages and disadvantages (e.g., Table 4). Similarly, although antisense therapy has progressed in recent years, there is still a high level of unpredictability in the art. This unpredictablity was summarized recently by Branch (TIBS 1998; 23:45-50). In particular, difficulties in ensuring that the oligo interacts with its single gene target versus other genes, and a variety of unexpected non-antisense effects, complicate the use of antisense compounds (e.g., summarized in Abstract). Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any pharmaceutical composition comprising an antisense nucleic acid are fraught with uncertainties.

Therefore, there is insufficient direction or objective evidence as to how to make and to how to use any agent which inhibits any cadherin-11 activity for the number of possibilities associated with the myriad of direct and indirect effects associated with various "inhibitory agents" and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

disadvantages are the need for repeated administration

Also, at issue is whether or not the claimed method would function "for treating a subject having an inflammatory joint disorder". The specification at page 4, lines 1-2 indicate that "inhibitory agent" such as monoclonal antibodies against cadherin-11 may be used "systemically". The problem would be how many times the administration of the antibodies are repeated and needed. The exemplification in the specification is drawn to the blocking of cadherin-11 from human type B synoviocytes using *in vitro* adhesion assays. Since there is no animal model system in the specification to treat an inflammatory joint disorder, it is unpredictable how to correlate test tube results with in vivo clinical trial. Since the method of treating an inflammatory joint disorder indices of administering to the subject a "cadherin-11 inhibitory agent" can be species- and model-dependent, it is not clear that reliance on the test tube studies accurately reflects the relative human efficacy of the claimed therapeutic strategy. In addition, it is not clear that reliance on the expression of cadherin-11 on certain inflammatory joint disorder would accurately reflects the relative ability of the claimed antibodies to treat inflammatory joint disorder in cadherin-11 expressing cells, encompassed by the claims. The specification does not adequately teach how to effectively treat an inflammatory joint disorder or reach any therapeutic endpoint in subjects by administering "cadherin-11 inhibitory agent". The specification does not teach how to extrapolate data obtained from test tube studies to the development of effective in vivo mammalian including human therapeutic treatment, commensurate in scope with the claimed invention.

Also, an effective treatment protocol for treating an inflammatory joint disorder in a subject is subject to a number of factors which enter the picture beyond simply the administration of cadherin-11 inhibitory agent locally to a synovium of the subject. Van Noort et al. (International Review of Cytology, 1998) indicate factors that effect autoimmune disease such as genetic, environmental and hormonal (Page 127, Paragraph 1). Inflammatory joint disorder is subject to variables beyond administration of cadherin-11 inhibitory agent to the subject. The ability of a host to suppress and thereby treat inflammatory joint disorder after establishing itself will vary depending upon factors such as the condition of the host and burden of inflammatory joint disorder. . Therefore, it is not clear that the skilled artisan could predict the efficacy of the "cadherin-11 inhibitory agent" exemplified in the specification. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 1, 3, 5, 6, 16 and 44-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method for treating a subject having a rheumatoid arthritis comprising administering locally to a synovium of the subject an anti cadherin-11 monoclonal antibody, however applicant is not in possession of a method for treating a subject having any inflammatory joint disorder comprising administering any cadherin-11 agent wherein the cadherin-11 inhibitory agent is any antibody, any cadherin 11 polypeptide, any nucleic acid molecule, or any antisense molecule that inhibits binding of cadherin-11 to any cadherin-11 counter receptor as disclosed in the specification on page 15, lines 24-34, page 19, lines 17-32, page 22, lines 5- 28 and page 28, lines 2-10. Consequently, conception in the above cases cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993).

Given the lack of a written description of *any* additional representative species for the claimed cadherin-11 inhibitory agents, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative member of species to describe the genus. Thus applicants were not in possession of the claimed genus. See *Regents of the University of California v. Eli Lilly & Co.*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 3, 5, 6, 8, 16 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,086,877 in view of U.S. Patent 5,597,725 (IDS reference No. A1) and Valencia et al (11-1998, IDS, reference C2).

The '877 patent teaches a method of treatment for rheumatoid arthritis (an inflammatory joint disorder) comprising administering to a patient an amount of an anti-Fas monoclonal antibody for treating rheumatoid arthritis and which reacts with a Fas antigen in rheumatoid synovial. The reference further teaches inhibition of synovial cells proliferation with a medical substance (such as anti-inflammatory agents), is thought to be a therapeutic agent for rheumatic disease (column 1 lines 34-36 in particular).

The claimed invention differs from the reference teachings only by the recitation of administering to a subject a cadherin-11 antibody as in the instant claim 8, the cellular function as in the instant claim 44, and cell proliferation as in instant claim 45.

The '725 patent teaches that different cadherins subclasses or combinations of subclasses are responsible for different cell-cell adhesion. Therefore cadherin is considered a direct counter receptor for another cadherin (column 2, lines 56-60 in particular). The '725 patent teaches methods for inhibiting binding of the cadherins to their natural ligands/antiligands by contacting a cadherin with an antibody (column 1, lines 20-22) such as a monoclonal antibody capable of specifically binding to cadherin-11 (column 111, lines 49-54 in particular).

Valencia *et al* teach the identification of cadherin-11 in type B synoviocytes derived from rheumatoid arthritis patients. In addition, Valencia et al. teach that cadherins maintain tissue

architecture and are important signaling molecules and the cadherins can mediate homophilic adhesion between synoviocytes, which could influence synovial proliferation and pannus invasion into cartilage or could engage in a heterophilic interaction anchoring lymphocytes within the synovial membrane parenchyma (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-Fas monoclaonal antibody taught by the '877 patent with the anti-cadherin-11 monoclaonal antibodiy taught by the '725 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the anti-Fas monclonal antibody taught by '877 patent with the anti- adherin-11 monoclonal antibody taught by the '725 patent because cadherin-11 monoclonal antibodies will inhibit binding of the cadherin-11 to it natural ligands/antiligands as taught by the '725 patent and hence inhibit homophilic adhesion between synoviocytes, which influences synovial proliferation and pannus invasion into cartilage as taught by Valencia *et al.*

Claim 5 is included because the administration of the cadherin-11 inhibitory agent locally to a synovium of the subject is well within the purview of one of ordinary skill in the art at the time the invention was made because cadherin-11 inhibitory agent would block cadherin-11 receptor in synoviocytes express cells and block its role in eroding the adjacent bone.

Claims 44-45 are included because Valencia et al reference teaches that cadherins modulate cellular functions in synoviocytes such as maintain tissue architecture and are important signaling molecules and the cadherins can mediate homophilic adhesion between synoviocytes, which could influence synovial proliferation and pannus invasion into cartilage or could engage in a heterophilic interaction anchoring lymphocytes within the synovial membrane parenchyma.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,086,877 in view of U.S. Patent 5,597,725 (IDS reference No. A1) and Valencia *et al* (11-1998, IDS, reference C2) as applied to claims 1, 3, 5, 6, 8,16 and 44-45 above, and further in view of U.S. Patent 5,886,026.

The teachings of the '877 and the '725 patents and Valencia *et al* reference have been discussed, supra.

The claimed invention differs from the combined reference teachings only by the recitation that the cellular function is factor secretion.

The '026 patent teaches that numerous enzymes are likely involved in the development of RA, collagenase (MMP-1) and stromelysin (MMP-3) play an important role in disease progression. These enzymes are capable of degrading type 11 collagen and proteoglycans respectively; the two major extracellular components of cartilage tissue. Cytokines are potent stimulators of collagenase and stromelysin production. Numerous cell types found in the arthritic joint such as synoviocytes are capable of synthesizing and secreting matrix metalloproteinases (MMPS) (column 30, lines 10-25 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-Fas monoclaonal antibody taught by the '877 patent with the anti-cadherin-11 monoclonal antibodiy taught by the '725 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to to substitute the anti-Fas monoclaonal antibody taught by the '877 patent with the anti-cadherin-11 monoclonal antibodiy taught by the '725 patent because cadherin-11 monoclonal antibodies will inhibit binding of the cadherin-11 to it natural ligands/antiligands as taught by the '725 patent and hence inhibit homophilic adhesion between synoviocytes, which influences synovial proliferation and pannus invasion into cartilage as taught by Valencia *et al* and which would modulate the secretion of a factor, MMPS in the synoviocytes as taught by the '026 patent. Therefore the monoclonal antibodies against cadherin-11 would modulate the cellular function such as MMPS secretion in the cell expressing cadherin-11 such as synoviocytes.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
April 15, 2002

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